Pilot-Scale Libraries for High-Throughput Screening

RFA Number: RFA-RM-05-014

Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov)

Components of Participating Organizations
This RFA is developed as an NIH Roadmap Initiative. All Institutes and Centers participate in Roadmap Initiatives. The RFA will be administered by the National Institute of General Medical Sciences (NIGMS), http://www.nigms.nih.gov on behalf of the NIH.

Announcement Type
New

Catalog of Federal Domestic Assistance Number(s)
93.859

Key Dates

Release Date: November 18, 2004
Letters Of Intent Receipt Date: January 14, 2005
Application Receipt Date: February 15, 2005
Peer Review Date: June-July 2005
Council Review Date : August-September 2005
Earliest Anticipated Start Date: September 15, 2005
Expiration Date: February 16, 2005

Due Dates for E.O. 12372
Not Applicable

Executive Summary

The Institutes and Centers (ICs) of the NIH invite applications for funding from the NIH Molecular Libraries Roadmap program for the generation of pilot-scale chemical diversity libraries. These libraries will be used for high-throughput biological screening by the Molecular Libraries Screening Center Network (MLSCN). Acceptable approaches will include: 1) chemical synthesis, including combinatorial chemistry/diversity-oriented synthesis; and/or 2) isolation and purification of bioactive compounds from natural sources such as microorganisms, marine organisms, or plants. Projects supported by this RFA should be driven by a strong scientific rationale that highlights the potential for in vivo and/or in vitro biological activity. NIH strongly encourages the submission of applications that target unexplored regions of chemical diversity space and as accordingly have particular promise for perturbing the functions of novel classes of biomacromolecules.

- The NIH intends to commit up to $3.5 million in FY 2005.
- Approximately 8-12 new grants will be made in response to this RFA.
- T he NIH Biotechnology Resource Grant (P41) award mechanism will be used. This is a one-time solicitation for three-year grants.
- Eligible organizations include for-profit or non-profit organizations; public or private institutions, such as universities, colleges, hospitals, and laboratories; units of State and local governments; eligible agencies of the Federal government; and domestic institutions/organizations. Foreign institutions/organizations are not eligible to apply.
- Eligible principal investigators include a ny individual with the skills, knowledge, and resources necessary to carry out the proposed research. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.
- There is no restriction on the number of applications that any individual or institution/organization may submit.

- The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Background

The NIH Roadmap is a series of initiatives designed to pursue major opportunities in biomedical research and gaps in current knowledge that cannot be addressed by any single NIH institute or center on its own, but that must be addressed by the agency as a whole. The goal is to enable the rapid transformation of new scientific knowledge into tangible benefits for public health (http://nihroadmap.nih.gov).

The Molecular Libraries and Imaging Initiative is a component of the ?New Pathways to Discovery? theme of the Roadmap. The goal of this initiative is to augment the toolbox for understanding the functionally interconnected networks of molecules that comprise cells and tissues, their interactions and regulation, and the combinations of molecular events that maintain health and lead to disease. The last decade has witnessed major breakthroughs in the identification of genes, gene products, metabolic pathways, and signaling pathways, as well as progress in miniaturization and robotics, enabling the development of high-throughput, highly specific, mechanism-based biological assays. The new assays have, in turn, revolutionized the discovery of small molecules with powerful physiological effects. While high-throughput screening (HTS) of small-molecule libraries is widespread in the pharmaceutical industry, the goal of the Molecular Libraries (ML) Roadmap Initiative is to facilitate the use of HTS and chemical libraries within the academic community. It is anticipated that the ML initiative will produce research tools (including novel small-molecule modulators of cellular function and phenotypic assays) to facilitate studies of biology and physiology (http://nihroadmap.nih.gov/molecularlibraries/index.asp).

For the most part, the academic community has not availed itself of the considerable potential of HTS to improve the understanding of biology. This is because most academic scientists have limited access to automated screening facilities and to libraries of structurally diverse compounds. The ML Initiative will establish and provide access to such resources and thus facilitate the broad application of HTS to research in the public sector.

The ML effort differs from HTS efforts in private industry in several ways. First, the NIH's interest is not limited to the identification of compounds with therapeutic properties. The range of the effort is much broader and will involve screening a greater diversity of small molecules in assays that will encompass a broader range of novel biological targets and activities. If successful, the ML Initiative will result in the identification of a very large number of compounds for use as probes to study cellular processes in health and disease. Second, the biological screening data, assay protocols, and chemical structures for compounds tested in the Molecular Libraries Screening Center Network (see below) will be publicly available for data mining via the PubChem database. Data-sharing with the larger scientific community represents a new paradigm that promises to: facilitate the understanding of basic biological mechanisms; identify new biological targets for evaluation in disease models; and shorten the timeline for ligand and tool discovery. Third, the ML Roadmap Initiative intends to facilitate, but does not directly include plans to engage in, the much longer term and more expensive process of drug development. It is anticipated that the initiative will complement private sector drug development efforts by contributing to the identification and validation of novel drug targets, as well as molecular structure classes with potential for development into therapeutics. The benefits to public health, especially for rare or marginalized disorders, are evident.

This particular RFA is part of the Chemical Diversity Technology Development effort, which in turn is a major component of the ML Initiative. Other components of the ML Initiative include: 1) the Molecular Libraries Screening Center Network (MLSCN): a national resource that will provide innovative HTS capacity for the identification of small, bioactive organic molecules using assays submitted by the research community, as well as synthetic chemistry to optimize these molecules as biological probes (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-017.html); 2) the NIH Small-Molecule Repository, which will house a collection of ca. 500,000 chemically diverse small organic molecules (see http://grants2.nih.gov/grants/guide/notice-files/NOT-RM-04-003.html); 3) PubChem: a public sector database that will archive the chemical structures and biological data generated by the MLSCN; and 4) the development of related technologies. In addition to this RFA, other technology development initiatives will aim to: a) stimulate the development of new methods for natural products chemistry (RFA-RM-05-013); b) facilitate the development and adaptation of innovative target- and phenotype-based assays that can be considered for use in screening by the MLSCN (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-012.html); c) develop new robotics and instrumentation for screening (see http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-020.html); and d) stimulate the development of predictive ADME/toxicology (absorption, distribution, metabolism, and excretion/toxicology) assays and algorithms (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-023.html).

Objectives of the Project

The ability to screen massive numbers of compounds quickly using HTS technologies continues to stimulate the demand for collections of novel small molecules. This demand is expected to increase markedly as the MLSCN becomes operational. Moreover, there is widespread agreement that increased access to chemical diversity is needed to target all of biological space (the total bounded set of biomolecular surface domains capable of interacting with small molecules) and thus increase the number of targets that are considered ?druggable.? The goal of this RFA is to solicit applications for chemical library generation, in order to increase the diversity and the utility of the collection in the NIH Molecular Libraries Small-Molecule Repository.

Pilot-scale libraries generated under this RFA will be submitted to the NIH Small-Molecule Repository and then to the MLSCN for evaluation by HTS. When a pilot-scale library exhibits an encouraging pattern of biological activity, a decision may be made to more fully explore the pertinent region of chemical structure space. Constructing these secondary libraries will fall outside the scope of this RFA.

Some of the chemistry methodologies to achieve the goals of this RFA exist currently, and libraries need only be made. In other cases, new methodology may be required. In contrast to the NIGMS Centers of Excellence in Chemical Methodologies and Library Development (CMLD), the focus of this RFA is on the generation of novel libraries rather than methodology development. Nevertheless, the ability to develop novel, library-related methodologies is likely to be important for success in meeting the goals of this RFA.

Approaches Being Sought to Achieve the Objectives

This RFA does not specify the means by which the libraries are to be assembled. In fact, any of several approaches may be envisioned, including: 1) high-throughput synthesis (HTSyn; commonly referred to as combinatorial chemistry, combichem, or diversity-oriented synthesis); 2) isolation and purification of compounds from living organisms (natural products), including compounds isolated from their natural sources, as well as natural products and natural product analogs made by the application of genetic engineering; and 3) target-oriented synthesis (including the synthesis of analogs of a natural product or other lead compound).

HTSyn is a process by which multiple compounds (chemical libraries) are generated simultaneously, in a predictable fashion, by techniques that involve parallel chemical transformations. HTSyn may use solid- or solution-phase reaction and separation techniques. A library may be small (e.g., a few compounds) or large (e.g., thousands or even millions of compounds), and it may focus on a narrow or wide range of "diversity space.?

Natural products may come from microorganisms or from higher organisms such as plants or marine invertebrates. Traditionally, natural products are isolated directly from their natural sources. However, recent developments have led to alternative sources of some natural products and natural product analogs. For instance, certain microbial metabolites may be produced by engineered organisms, including heterologous hosts. Similarly, by genetic manipulation of the genes that encode the biosynthetic machinery, pathways may be adapted so as to yield analogs of certain natural products.

The total synthesis of complex molecules, particularly natural products, long has been a dominant theme in organic chemistry. The rationale for total synthesis is rooted in the fact that until the latter part of the 20th century, natural product structures had to be deduced from a preponderance of indirect evidence. Thus, chemical degradation eventually would afford fragment molecules that were simple enough to be identified, and when considered in the context of the chemical reactions that had been employed, a structure could be inferred for the parent natural product. Given the indirect nature of this process, as well as the sometimes unanticipated outcomes of the degradation reactions, the ultimate proof would be the de novo synthesis of the proposed structure and demonstration that the natural and synthetic materials indeed were identical. However, during the last 40 years, analytical techniques such as nuclear magnetic resonance spectroscopy, mass spectrometry, and X-ray crystallography have become so powerful, sensitive, and widely available that total synthesis rarely is required to complete or even confirm a structure proof.

Today, in addition to providing a platform for the development of new chemical methodologies, a prime motivation for the synthesis of complex molecules is the investigation of biological activities. Accordingly, many synthetic strategies are devised so as to be short (i.e., relatively few reaction steps), efficient (i.e., high-yielding), and readily adaptable to the synthesis of key analogs. Ideally, such analogs allow mechanistic hypotheses to be addressed and/or allow pharmacophore characterization.

Of particular interest to the NIH are libraries composed of molecules with versatile chemical ?handles? that would readily allow tagging with suitable reporter groups. Thus, prior to use in a screening assay, a given ?taggable? library could be customized by outfitting the constituent molecules with whatever reporter group happened to be most appropriate for the assay in question.

Experts have estimated that the theoretically accessible extent of "chemical diversity space" is 10(E60) small-molecule structures (i.e., molecular weights up to 500). By comparison, fewer than 10(E8) small-molecules have ever been synthesized or isolated from natural sources. In view of the challenge, applicants should describe the process by which regions of chemical diversity space will be selected for study, as well as the general rationale to be used in planning pilot-scale libraries. It should be noted that PubChem may be useful for gauging the need for libraries representing particular regions of chemical diversity space.

While libraries submitted in response to this initiative need not be ?drug-like? in the usual sense (since NIH's goal is not drug discovery), factors such as solubility as well as chemical stability under HTS and storage conditions are very important. Inherently reactive functional groups (e.g., alpha-haloketones, acid chlorides, or aziridines) are undesirable.

A typical pilot-scale library might include 10-100 compounds, in order to afford adequate structural diversity for evaluation of the library design concept and to provide a basis for deciding whether further exploration of the particular region of chemical diversity space is warranted. In the interest of minimizing false positives in HTS assays, a high premium will be placed on analytical purity. Applicants should state specifications for acceptable levels of purity (ordinarily, at least 90%) and should describe the analytical methods that will be used to assess purity as well as compound identity. Analytical data must accompany submissions to the NIH Repository.

The preferred format for submission will be determined through discussions with the NIH Small-Molecule Repository. In all likelihood, it will be dry films or powders, or solutions in dimethylsulfoxide (DMSO), and sample containers will be provided by the Repository. It will be the responsibility of the grantee to verify that none of the compounds submitted to the NIH Repository is covered by an existing patent or patent application. Written certification to this effect must be provided to the NIH before compounds can be accepted.

As mentioned above, compounds in the NIH Repository will be subjected to a variety of HTS assays. Accordingly, each compound must be supplied in a quantity of no less than 10 mg. When HTS assay results indicate that a compound has interesting and/or useful properties, it is likely that additional quantities and/or additional analogs will be needed. While supply of these additional materials is not a specific goal of this RFA, it is highly desirable that resupply of compounds and the generation of analogs be readily achievable. For this purpose, compounds submitted to the repository must be accompanied by documentation indicating their origin, such as (in the case of synthetic molecules) synthesis protocols. It is recognized that the generation of analogs may be substantially easier for synthetic compounds than for natural products, and so the uniqueness of natural product libraries as well as a compelling rationale for novel biological activity may be considered as compensating factors.

NIH is not specifying the number of libraries to be generated and submitted each year by each grantee. On the one hand, it is a goal of the ML Roadmap to assemble a large number of unique, potentially bioactive small molecules for the compound repository. Each applicant should provide a well-justified estimate of the total number of compounds and the number of unique libraries to be submitted to the Repository each year. These estimates will provide a basis for evaluation of the grant application as well as a benchmark for evaluating the actual output of each grantee. While a substantial rate of library production is desirable, it is especially important that the libraries generated and submitted under this RFA be thoughtfully designed, well-characterized, and provided in good quantity (vide supra). It is likely that libraries submitted to the Repository by grantees under this RFA will be accepted into the NIH small-molecule collection; however, this will not always be the case. For example, if a new library falls largely in a region of chemical diversity space that already is adequately represented in the collection, then it is unlikely that the new library will be accepted.

Applicants must discuss their proposed methodologies and strategies for the generation of high-quality libraries. The following are examples of topics that should be addressed: chemical synthesis strategies; amenability to the production of second generation compound analogs; compound purification; sample handling; qualitative and quantitative analysis of libraries and individual compounds; sample storage; the archiving of analytical data; and plans for public dissemination of information on the methodologies that are used.

Project Oversight

As part of the larger Molecular Libraries and Imaging Roadmap Initiative, projects that are funded under this RFA are subject to oversight and evaluation of each aspect of the effort.

THE MOLECULAR LIBRARIES AND IMAGING IMPLEMENTATION GROUP (MLIIG). The MLIIG comprises the Directors of the National Human Genome Research Institute (NHGRI), the National Institute of Mental Health (NIMH), and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) as well as the NIH staff who coordinate the major components of the Molecular Libraries and Imaging Roadmap Initiative. The MLIIG will provide overall guidance.

THE PILOT LIBRARIES PROJECT TEAM. The Project Team will be the operational governing body for the initiative and will include NIH staff from various Institutes and Centers who are actively involved in the management and implementation of this Roadmap initiative. The Project Team will report to the MLIIG.

In addition to these oversight committees, grantees under this RFA will interact with the MLSCN Compound Acquisition Working Group. This group will oversee the operation of the Repository and the management of the NIH Small-Molecule Collection. It also will evaluate proposals for the acquisition of small-molecules from public and private sources for the Repository. Recommendations on which of the libraries generated under this RFA will be accepted by the Small-Molecule Repository will by made by this working group and will be communicated to the Pilot Libraries Project Team. As mentioned above, while it is likely

that libraries submitted under this RFA will be accepted into the Repository, acceptance will not be automatic. Also, the NIH collection will be dynamic, and compounds may be eliminated from the collection if they are deemed expendable.

Section II. Award Information

1. Mechanism of Support

This funding opportunity will use the NIH Biotechnology Resource Grant (P41) award mechanism. This mechanism is used to support the development of research resources that will be available to qualified investigators without regard to the scientific disciplines or disease orientations of their research activities. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Any future, unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures.

2. Funds Available

On behalf of the NIH Roadmap, the National Institute of General Medical Sciences intends to commit up to $3.5 million dollars in FY 2005 to fund approximately 8-12 new grants in response to this RFA. An applicant may request a project period of up to three years.

Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the National Institute of General Medical Sciences provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds and the receipt of a sufficient number of highly meritorious applications.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local government
- Eligible agencies of the Federal government

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his/her institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

2. Cost Sharing

N/A

3. Other-Special Eligibility Criteria

N/A

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format . For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 05/01) must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at http://www.dnb.com. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

See Section VI.2 Administrative Requirements for additional information.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form, and the YES box must be checked.

3. Submission Dates

3.A. Receipt, Review and Anticipated Start Dates

Letter of Intent Receipt Date: January 14, 2005
Application Receipt Date(s): February 15, 2005
Peer Review Date: June-July 2005
Council Review Date: August-September 2005

3.A.1. Letter of Intent

Prospective applicants are asked to submit a letter of intent that includes the following information:

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIGMS staff to estimate the potential review workload and plan the review.

The letter of intent is to be received by January 14, 2005.

The letter of intent should be sent to:

John M. Schwab, Ph.D.
Division of Pharmacology, Physiology, and Biological Chemistry
National Institute of General Medical Sciences
45 Center Drive, Room 2As.43A MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5560
FAX: (301) 480-2802
Email: schwabj@nigms.nih.gov

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and three signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

At the time of submission, two additional copies of the application and all copies of the appendix material must be sent to:

Helen R. Sunshine, Ph.D.
Chief, Office of Scientific Review
National Institute of General Medical Sciences
45 Center Drive, Room 3AN.12E
MSC 6200
National Institutes of Health
Bethesda, MD 20892-6200
Telephone: (301) 594-2881
FAX: (301) 480-8506
Email: sunshinh@nigms.nih.gov

The RFA label available in the PHS 398 application instructions must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf.

3.C. Application Processing

Applications must be received **on or before the application receipt date** listed in the heading of this funding opportunity. If an application is received after that date, it will be returned to the applicant without review. Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the National Institute of General Medical Sciences and the Pilot Libraries Project Team. Incomplete and/or non-responsive applications will not be reviewed.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be prepared as a NEW application. That is, the application for the funding opportunity must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application. Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight (8) weeks.

4. Intergovernmental Review

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm (See also Section VI.3. Award Criteria)

6. Other Submission Requirements

Plan for Sharing Research Data

Since the inception of the ML Roadmap, NIH has emphasized that in order to yield the maximum benefit, all physical and intellectual research resources should be publicly available. There are strong scientific arguments supporting this position. Small-molecule probes that selectively interact with biological targets are key research tools for understanding the functions of proteins and for elucidating biological pathways. A collection of such probes that would allow the comprehensive study of all of the proteins and other gene products encoded by the human genome would be an invaluable contribution to biomedical research. It will take the combined efforts of researchers in the public and private sectors many years of using small-molecule probes to completely characterize the biology of genes and proteins in health and disease, and then to use that information to

develop approaches that will improve public health. Clearly, the open sharing of data, research tools, and resources will lead more rapidly to the identification and validation of novel targets for drug discovery, and will facilitate the rapid development of therapeutics by both the private and public sectors, with resulting benefits to public health, especially for rare or marginalized disorders.

All applicants must include a plan for sharing research data in their application, regardless of the level of funding that is being requested. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score.

Sharing Research Resources

Guidance for Community Resources The following data and materials generated or developed through the ML Roadmap initiative are expected to be community resources: (1) primary data from HTS and from secondary screens; (2) protocols for assays implemented in the MLSCN; (3) the chemical structures of compounds tested in the MLSCN; and (4) the optimization chemistry protocols for probe development conducted within the MLSCN centers. In keeping with this approach, NIH expects that (1) all libraries and individual compounds submitted to the NIH under this RFA; (2) data derived from biological screening of these compounds; and (3) protocols for obtaining these compounds (via synthesis, biosynthesis, or by isolation from biological sources) will be made readily available and accessible, consistent with other facets of the ML Roadmap.

It is well established in the scientific community that hits in random HTS of chemical libraries such as those in the NIH small-molecule collection almost invariably require extensive medicinal chemistry optimization in order to be useful for *in vivo* investigational, much less for human therapeutic, purposes. NIH is concerned that patents on compounds that give rise to early-stage HTS hits would be premature, could have a chilling effect on the development of future substantive inventions, and thus could interfere with the broad utilization of early-stage biological and chemical information, which is the purpose of the ML initiative. Consistent with this concern, discussions with investigators in both the public and private sectors have indicated that those who otherwise might be interested in optimizing and developing these compounds with therapeutic intent might not utilize them if they were patented. It is the NIH's opinion that the objectives of the ML program would be served best by facilitating future innovation based on the compounds in the NIH collection and their use in biological systems, enabling the production of small-molecule probes with more advanced properties. To the extent that early patent filing and restrictive licensing could interfere with this scenario, such approaches would not be consistent with NIH's intent for the ML program.

On the other hand, it is NIH's hope and expectation that the analysis of HTS data from the MLSCN (which will be freely available via PubChem) will spur efforts to develop second-generation compounds with practical value, such as more advanced tools for biological investigation, or drug leads. Optimized, second generation compounds that are pursued independent of this RFA would not be subject to any special IP considerations as described herein. Rather, NIH would encourage appropriate intellectual property (IP) protection of compounds at those later stages of development.

It is NIH's understanding that the utility of the resources and data generated by the ML initiative will be maximized if they are treated as community resources and made broadly available, consistent with achieving the goals of the ML Roadmap. While NIH recognizes that under the Bayh-Dole Act, awardees have the right to elect title to subject inventions and seek appropriate IP protection, the data sharing and IP plans should take all of the above considerations into account. Applicants should provide clear explanations and rationales for their plans, especially for any proposed plan that involves principles differing from those described in this RFA. **Guidance for IP and Accessibility of Technology Development Resources** A separate component of the IP plan should address any other data and resources that are expected to be generated by the grantees under this RFA. These may include, but are not limited to: chemical methodology, chemical instrumentation, software, etc. NIH encourages applicants to consider inclusion of "non-assert" language in IP plans for all potentially patentable inventions to ensure that, while an institution might apply for a patent on an invention, the institution would not attempt to enforce that patent against organizations utilizing the technology for research purposes. **Review of Plans** The data sharing and IP plans in the application will be evaluated by the Scientific Review Group using the principles and expectations detailed in this RFA, but will not be considered in the priority score. Following the review, in the case of those applications being considered for funding, program staff will negotiate a final version of plans for data sharing and IP to ensure accessibility of research resources. Applicants' plans for maximizing the public use of the data and resources generated under this RFA will be a major award criterion. Finalized plans will be made terms and conditions of any grant awarded under this RFA. If the goals of the ML Roadmap are not being met using this approach, NIH will consider using a determination of exceptional circumstances (DEC) under future awards to restrict or eliminate the right of parties to elect title to subject inventions. NIH policy requires that grant awardees make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication, as per the NIH Grants Policy Statement (http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131). Investigators responding to this funding

opportunity should include a plan for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan and any related data sharing plans will be considered by Program staff of the funding organization when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report. (PHS 2590). See Section VI.3. Award Criteria.

Section V. Application Review Information

1. Criteria

N/A

2. Review and Selection Process

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIGMS in accordance with the review criteria stated below.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- Receive a written critique
- Receive a second level of review by the National Advisory General Medical Sciences Council.

In addition to technical merit, programmatic considerations such as the diversity of experimental approaches may enter into funding decisions made under this RFA.

3. Merit Review Criteria

The goals of NIH supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance . Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field? How likely are the proposed strategies to result in the discovery of small molecules with novel and significant bioactivities?

2. Approach . Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Will the proposed approach afford compounds in acceptable quantities (at least 10 mg/compound) and acceptable purities (ordinarily, at least 90%)? Are the proposed analytical methodologies adequate for demonstrating the quality (i.e., identity and purity) of the compounds to be submitted to the NIH? Is there an adequate plan to ensure that compounds submitted to the NIH will be physically and chemically compatible with high-throughput screening? Are issues of resupply and producing analogs dealt with adequately? Will a substantial number of unique libraries and new compounds be provided, and is the applicant's estimate well-justified? Will the design of each library be based upon a sound and insightful rationale? Are the proposed methods for sample handling and storage adequate?

3. Innovation . Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

4. Investigators . Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

5. Environment . Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

3.A. Additional Review Criteria:

N/A

3.B. Additional Review Considerations

The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

3.C. Sharing Research Data

The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The presence of a data sharing plan will be part of the terms and conditions of the award. NIGMS and ML Roadmap staff will be responsible for monitoring the data sharing policy.

3.D. Sharing Research Resources

NIH policy requires that grant awardees make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://ott.od.nih.gov/newpages/rtguide_final.html. Investigators responding to this funding opportunity should include a sharing research resources **plan** addressing how unique research resources will be shared or explain why sharing is not possible. See Section IV.6 (above) for a detailed discussion of the guidelines for sharing of research resources.

The adequacy of the resources sharing plan will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing plans with the Principal Investigator before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report. (PHS 2590). See Section VI.3. Award Criteria.

Section VI. Award Administration Information

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1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm.

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the grants official at the applicant organization, electronically via the NIH Commons, via e-mail, or via U.S. mail, depending upon the capabilities of the applicant organization. The notice of award signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

2. Administrative Requirements

All NIH Grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm.

3. Award Criteria

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance to program priorities

4. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually: http://grants.nih.gov/grants/funding/2590/2590.htm and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific / Research Contact:

John M. Schwab, Ph.D.
Division of Pharmacology, Physiology, and Biological Chemistry
National Institute of General Medical Sciences
45 Center Drive, Room 2As.43A MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5560
FAX: (301) 480-2802
Email: schwabj@nigms.nih.gov

2. Peer Review Contact:

Helen R. Sunshine, Ph.D.
Chief, Office of Scientific Review
National Institute of General Medical Sciences
45 Center Drive, Room 3AN.12P MSC 6200
National Institutes of Health
Bethesda, MD 20892-6200
Telephone: (301) 594-2881
FAX: (301) 480-8506
Email: sunshinh@nigms.nih.gov

3. Financial or Grants Management Contact:

Ms. Antoinette Holland
Grants Management Office
National Institute of General Medical Sciences
National Institutes of Health
45 Center Drive, Room 2AN.50B MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5132

FAX: (301) 480-2554
Email: hollanda@nigms.nih.gov

Section VIII. Other Information

Required Federal Citations

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible, http://grants.nih.gov/grants/policy/data_sharing.

Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Public Access to Research Data through the Freedom of Information Act:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:
The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Department of Health
and Human Services

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892